SCREENING FOR FAMILIAL HYPERCHOLESTEROLAEMIA IN ADULTS IN THE UK AND THE UK NSC SCREENING CRITERIA

Anne Mackie[1], Steve E Humphries[2] and H Andrew W Neil[3], On Behalf of the Simon Broome Register Committee.

1. UK National Screening Committee.
2 Centre for Cardiovascular Genetics, BHF Laboratories, Department of Medicine, University College London, Rayne Building, 5 University Street, London WC1E 6JF
3 Professor of Clinical Epidemiology, NIHR School of Primary Care Research, Division Public Health & Primary Health Care, University of Oxford , OX2 7LJ

SUMMARY

Modelling suggests that universal screening for Familial Hypercholesterolaemia (FH) is not cost-effective and therefore a universal screening programme is not recommended. Best evidence currently supports cascade testing; tracing family members to identify affected relatives of known FH patients. However across the UK various schemes are in place to assess and modify cardiovascular risk in adults and will inevitably detect more people with FH which will complement cascade testing. It is doubtful whether existing lipid clinics could cope with the extra workload without investment.

FH - THE CONDITION

1. The condition should be an important health problem

The prevalence of heterozygous FH in the UK population is estimated to be 1 in 500, which means that approximately 120,000 people are affected. The elevated serum total and low density lipoprotein (LDL) cholesterol concentration that characterises heterozygous FH leads to a greater than 50% risk of coronary heart disease in men by the age of 50 years and at least 30% in women by the age of 60 years.[1]

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

The epidemiology and natural history of FH is well understood and has been extensively reviewed [2]. By definition all patients with FH have elevated levels of LDL cholesterol which is a detectable risk factor in childhood, and therefore in heterozygous FH there is a long enough latent period before the onset of CHD for affected individuals to be offered effective treatment[3]. Early detection and treatment with statins has been shown to reduce morbidity and mortality [4].

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

As the disease is asymptomatic until presentation with CVD or physical manifestations there are no primary preventative activities for individuals other than the routine measures for reduction of CVD in the general population. For those people with affected family members cascade screening is recommended. There is clear evidence that this is not being carried out in a systematic way and is therefore not being implemented as effectively as recommended[5]

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

FH can be caused by mutations in either the low-density lipoprotein receptor gene (*LDLR*), the apolipoprotein B-100 gene (*APOB*) or the proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*) [6]. Using routine DNA diagnostic techniques that are available in many accredited NHS laboratories, it is possible to identify a causative mutation in up to 80% of patients with the strongest clinical diagnosis (Definite FH, see box 1)

Results from cascade testing have found that the majority of people find it acceptable, though studies have found a small proportion of people with heterozygous FH had some degree of anxiety and regretted that they were informed of the diagnosis of heterozygous FH. However, the most affected individuals favoured family screening for heterozygous FH [7], and most families had not experienced psychosocial problems associated with the diagnosis of familial hypercholesterolaemia[8] A UK RCT of the psychological impact of DNA testing in families with FH indicated no major impact over and above that associated with testing using lipid levels [9]

THE TEST

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

A venous or capillary blood specimen for measurement of total cholesterol is the initial screening test. An elevated initial screening test result requires confirmation with a repeat sample in the fasting state for measurement of total cholesterol, HDL-cholesterol and triglyceride. FH is suspected when Total Cholesterol levels and more particularly LDL-C levels are found over the UK Simon Broome cut-offs in at least 2 fasting blood samples, as recommended by NICE CG71 [10]

LDL-C levels in the UK population are well documented, and are available by gender and age cut-offs (e.g. from the Health Survey of England and Wales). There are, however, no 100% accurate diagnostic criteria for FH. There is an overlap between the frequency distribution for LDL-cholesterol in the general population and that for patients with FH, which leads to false positive and false negative diagnostic rates of between 8–18%.[11] The diagnostic cut-points can be refined by taking account of age and should be specific to particular populations.

As shown in Box 1, the Simon Broome diagnostic criteria recommended by NICE CG71, stipulates total and LDL levels that are different for adults and children. and to classify patients into definite FH or possible FH. A diagnosis of definite FH is made if the patient has elevated cholesterol levels and tendon xanthoma, while a diagnosis of possible FH is made if the patient has elevated cholesterol levels and a family history of hypercholesterolaemia or heart disease.

A **Definite familial hypercholesterolaemia is defined as:**

- total cholesterol greater than 6.7 mmol/l or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/l in a child aged younger than 16 years or total cholesterol greater than 7.5 mmol/l or LDL-C greater than 4.9 mmol/l in an adult (levels either pre-treatment or highest on treatment) **plus**
- tendon xanthomas in patient, or in first-degree relative (parent, sibling or child), or in second-degree relative (grandparent, uncle or aunt) **or**
- DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

B **Possible familial hypercholesterolaemia is defined as:**

- total cholesterol greater than 6.7 mmol/l or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/l in a child aged younger than 16 years or total cholesterol greater than 7.5 mmol/l or LDL-C greater than 4.9 mmol/l in an adult (levels either pre-treatment or highest on treatment) **and at least one of the following**
- family history of myocardial infarction: younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative **or**
- family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child or sibling aged younger than 16 years.

Patients with possible FH are more numerous in most UK clinics than those with xanthomatous (i.e. definite) FH. Since the criteria for possible FH are less specific than for definite FH, possible FH will inevitably include some patients with polygenic hypercholesterolaemia. It is, however, important to distinguish between acquired polygenic hypercholesterolaemia and FH. Patients with FH have sustained elevation of LDL cholesterol from birth and are at a higher risk of coronary disease for any given LDL concentration. Consequently, they warrant more aggressive cholesterol-lowering therapy than suggested by published risk charts based on their age, sex, LDL levels, and other coronary risk factors.

7. The test should be acceptable to the population.
22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

Measurement of plasma lipid levels to asses an individual's CVD risk are now widely accepted in the general population as a result of recent health promotion campaigns. To examine how applicable ***cascade testing*** is to mainstream health services, the Department of Health funded an audit [5] study to determine the efficiency of cascade testing in a Lipid Clinics operating within the National Health Service. This reported

that cascade testing using lipid measures was feasible and acceptable, with a proband response rate of 70%, and 76% of the first degree relatives who lived in the catchment area coming forward for testing.

A report from Norway suggested that the majority of the public were in favour of screening in principle [12] and Norway, Spain and Holland [13] have all run a systematic cascade screening programme for more than five years.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The care pathway for identified FH patients is outlined in NICE CG71 10

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

A commercially available and accredited 20-mutation test kit is in use in diagnostic laboratories, which tests for the common *APOB* and *PCSK9* mutations and 18 common LDLR mutations [14]. It detects roughly 50% of all mutations that would be identified by a complete LDLR gene screen, and is considerably cheaper. A full gene screen for FH is available in 2-3 NHS diagnostic laboratories in the UK

THE TREATMENT

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

Statin treatment is highly effective in lowering LDL-C in FH patients, and a recent report indicates that, among patients identified before the development of CHD, after statin treatment their subsequent life expectancy is no less than in individuals in the general population [10]
Because of their untreated extreme risk it is not ethically acceptable to perform a randomised placebo controlled clinical outcome trials of statin treatment in FH patients and none have been conducted. NICE CG71 accepted that recommendations for clinical management for FH should be based on evidence from observational studies and extrapolation from the results of clinical trials of lipid lowering drug therapy conducted in patients with polygenic hypercholesterolaemia, as well as from evidence using carotid intima-medial thickness as a surrogate outcome, and from a small number of prospective observational studies.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

The 2008 NICE guidelines (CG71) on the identification and management of FH [10] outline policies covering which individuals should be offered treatment and the appropriate treatment to be offered. Briefly, CG71 recommends that, in general, the diagnosis and management of FH is best coordinated by a specialist. The recommendations stipulate diagnostic cut-points and specify further investigations. Regardless of age, a positive screening test must be confirmed by measurement of a fasting lipid profile and secondary causes of hypercholesterolaemia must be excluded. Treatment options are, in order of efficacy and acceptability, HMG CoA (hydroxymethylglutaryl co-enzyme A) reductase inhibitors (statins), ezetimibe - a cholesterol absorption inhibitor bile acid sequestrants (resins), and diet.

Life-style changes in diet exercise and particularly smoking cessation are emphasised. Importantly the guidelines recommend the adoption of systematic family tracing (cascade screening) based on DNA mutation information if available and LDL-C levels if not. The guidelines suggest that children should be tested by the age of 10 years, and that the age for testing should take account of parental wishes, the age of onset of coronary disease in index case and other affected family members, and the treatment options available dependent on the age of the child.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

Clinical management of FH patients is recommended by NICE CG71 to be managed primarily in lipid clinics with formalised shared care arrangements with General Practice after optimisation of lipid-lowering treatment. Data from the RCP National FH Audit [5] suggests that patients who have been identified are being appropriately treated in lipid clinics. However if cascade screening were to be fully implemented these clinics would need a huge expansion in numbers, there is limited access to DNA testing and a shortfall in child focussed treatment centres.

THE SCREENING PROGRAMME

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

No such evidence is available for FH.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

Cascade testing, that is contacting first degree relatives of FH probands (index cases) and identifying affected relatives by their elevated cholesterol levels, as a method of

case-finding has been used extensively in other countries in Europe. To examine how applicable this was to mainstream health services, the Department of Health funded a study [15], to determine the efficiency of cascade testing in Lipid Clinics operating within the National Health Service. The majority (~70%) of index cases participated; the proportion was lower when patients had been discharged from the clinics, and in metropolitan areas. On average, 34% (range 13%-50%) of relatives lived outside the catchment area of the clinics. and could not attend the nurse-led FH clinics. Seventy-six percent of previously untested relatives, who lived in the catchment area of the clinic, came forward to be tested. A third of the relatives coming forward for testing were children ≤16 years of age. Overall the data support the view that cascade screening is acceptable and feasible in the UK.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

In a cost effectiveness analysis carried out in 2002 Marks et al [16] examined (i) universal screening; (ii) opportunistic screening in primary care; (iii) screening of premature myocardial infarction admissions; and (iv) tracing family members of affected patients. They concluded that tracing family members to identify affected relatives of known FH patients would be a cost-effective strategy (£3097 per life year gained) and only 2.6 individuals need to be screened to identify one case at cost of £133 per case detected. If the genetic mutation was known within the family then the cost per life year gained was only slightly increased by genetic confirmation of the diagnosis (£4914). For each strategy it was more cost effective to screen younger people and women. Targeted strategies were more expensive per person screened, but the cost per case detected was lower. While population screening of 16 year olds was as cost effective as family tracing (£2777), this was based on the assumption that such a program would be as clinically, socially and ethically acceptable to health professionals and the public, and that there was at least a 55% uptake amongst the 16-year olds invited for screening. If such a programme is to be proposed additional data to support or refute these assumptions directly will be needed.

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

Data from the RCP FH Audit [5] suggests that patients who have been identified are being appropriately treated in lipid clinics. However if cascade screening were to be fully implemented these clinics would need a considerable expansion in numbers, there is limited access to DNA testing and a shortfall in child focussed treatment centres.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

NICE have laid out the protocols and standards for the management of a cascade screening programme. In the RCP National FH audit data was collected regarding key aspects of the cascade process as no universal screening programme exists there are no such standards for population screening.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

Such information is widely available from such organisations as BHF and HEARTUK and is in wide use already in UK lipid clinics [5].

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

Policy Implications

Full population screening for FH in adults does not seem on the balance of available evidence to fulfil the criteria for a screening programme. However the advent of the NHS Health Check [17] means that all adults between 40 and 74 will be called for a cardiovascular risk assessment which will include a test for cholesterol levels. This process (if managed in a systematic and conscientious manner should detect the majority of people with FH and trigger cascade testing for family members wishing to participate. The national guidance for the NHS Health Check includes recommendations to consider FH in anyone with a cholesterol level of 7.5 and refers to the NICE guidance.

Given this policy environment it seems sensible to simply refer any proposals for a universal screening programme for adults in that age group to the NHS Health Check process rather than assess a screening programme against UK NSC criteria on a regular basis.

Acknowledgments
The Simon Broome Register committee includes Dr Nigel Capps, Dr Mary Seed, Prof Paul Durrington, Dr Paul Miller, Dr Ian McDowell and Prof John Betteridge. SEH acknowledges BHF support (RG2008/008) and grants from the Department of Health.

1. Scientific Steering Committee on behalf of The Simon Broome Register Group. The risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991;**303**:893-6.
2. Marks D, Thorogood M, Neil HAW *et al*. A review on the diagnosis, natural history and treatment of familial hypercholesterolaemia. *Atherosclerosis* 2003; 168 (1):1-14
3. Neil A, Cooper J, Betteridge J *et al*. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *European Heart Journal* 2008; 29(21):2625-3

4. Scientific Steering Committee on behalf of The Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for patient management. *Atherosclerosis* 1999; 142:105-12
5. Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, Cramb R, Egan S, Everdell R, Ferns G, Jones A, Marenah CB, Marples J, Prinsloo P, Sneyd A, Stewart MF, Sandle L, Wang T, Watson MS, Humphries SE; Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem. 2009 Jan;46(Pt 1):24-32.
6. http://www.rcplondon.ac.uk/resources/audits/FH
7. Humphries SE, Whittall RA, Hubbart CS *et al.* Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. *Journal of Medical Genetics* 2006; 43:943-9
8. Andersen LK, Jensen HK, Juul S *et al*. Patient attitudes to detection of heterozygous familial hypercholesterolaemia. *Archives of Internal Medicine* 1997; 157:553-60
9. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's concerns. *Acta Paediatrica* 1996; 85: 1307-13
10. Marteau T, Senior V, Humphries SE, Bobrow M, Cranston T, Crook MA, Day L, Fernandez M, Horne R, Iversen A, *et al*.: Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *American Journal of Medical Genetics A* 2004, **128A**(3):285-293.
11. DeMott K, Nherera L, Shaw EJ et al. Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. http://guidance.nice.org.uk/CG71
12. Leonrad JV, Whitelaw AG, Wolff OH, Lloyd JK, Slack J. Diagnosing familial hypercholesterolaemia in childhood by measuring serum cholesterol. *BMJ* 1977;**1**:1566-8
13. Tonstad S, Vollebaek LE, Oxe L. Screening for familial hypercholesterolaemia in relatives. *Lancet* 1995; 346:1438
14. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet 2001;357:165-8
15. Taylor A, Patel K, Tsedeke J, Humphries SE, Norbury G. Mutation screening in patients for familial hypercholesterolaemia (ADH). Clin Genet. 2010 Jan;77(1):97-9.
16. Marks D, Wonderling D, Thorogood M *et al*. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 2002; 324:1303
17. NHS Health Check: Vascular Risk Assessment and Management Best Practice Guidance. http://www.dh.gov.uk/en/Publicationsand statistics/Publications/PublicationsPolicyAndGuidance/DH_097489